The NICE COVID-19 rapid guideline on haematopoietic stem cell transplantation: development, implementation and impact

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Keywords: haematopoietic stem cell transplantation, autologous, allogeneic, COVID-19, SARS-CoV-2, donor.

A new coronavirus *SARS-CoV-2* emerged at the start of 2020 with rapid worldwide spread. It is the causative agent of Coronavirus Disease 2019 (COVID-19). The resulting pandemic has been challenging for centres undertaking autologous and allogeneic haematopoietic stem cell transplants (HSCT). One of the main risks in HSCT is infection susceptibility, including viral infections, which are often more severe and life-threatening.[1]

In response to the COVID-19 pandemic, the National Institute for Health and Care Excellence (NICE) published the first version of the COVID-19 rapid guideline for HSCT (NG164) on 1 April 2020[2]; this was updated on 29 July 2020 in response to the changing context of the pandemic. The British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) and the European Society for Blood and Marrow Transplantation (EBMT) also developed detailed guidance to support transplant centres.[3-5]

This paper describes the development and update processes for NICE NG164, detailing the rationale behind the recommendations, implementation and the impact of COVID-19 on HSCT activity in the UK compared with 2019, based on registrations in the BSBMTCT registry. The full NICE guidance can be obtained from: https://www.nice.org.uk/guidance/ng164.

Process and methods for guideline development

NICE NG164 was developed jointly by NICE and NHS England and NHS Improvement (NHSE&I) in March 2020. The main stages of development included scoping, appointing an independent advisory expert panel, conducting evidence reviews, drafting recommendations, as well as targeted peer review through stakeholder consultation. The cross-speciality independent clinical advisory panel for HSCT included experts from the BSBMTCT, the NHSE&I Clinical Reference Group (CRG) for Blood and Marrow Transplantation (BMT), supported by the NICE guideline development team.

The clinical review considered how the delivery of HSCT services should be managed for patients and donors during the COVID-19 pandemic and how to mitigate risks of COVID-19, at all stages of HSCT. An initial literature search was undertaken on 24 March 2020, in the early days of the pandemic when little information was available on COVID-19. A targeted approach was taken to identify published and preprint guidance and evidence. The recommendations were informed by a combination of evidence and expert panel consensus. The final guideline scope and equality impact assessment and the interim process and methods manual are published on the NICE website.[6] An update of the NICE guideline was published, incorporating advice based on emerging evidence on the *SARS-CoV-2* virus, the epidemiology and clinical impact.[7] A surveillance approach was implemented following publication involving frequent searches of literature and guidance, and a pragmatic intelligence gathering approach to identify other information which could impact on recommendations, such as changing COVID-19 alert levels and implementation feedback.

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 British Journal of Haematology, 2021, **192,** 467–473 doi: 10.1111/bjh.17280

Communicating with patients and minimising risk

Patients undergoing HSCT experience significant anxiety and distress.[8] The Shielding Behavioural Survey undertaken by the Office for National Statistics (ONS) in June 2020 showed that 35% of people who are clinically extremely vulnerable reported that their mental health had become slightly worse (29%) or much worse (6%).[9] A survey undertaken by Anthony Nolan, using the same wording as the ONS survey, showed that 79/139 (57%) of respondents reported that their mental health had become slightly worse (57/139, 41%) or much worse (22/139, 16%) as a result of the coronavirus pandemic (Anthony Nolan, personal communication).

To support their mental wellbeing, the guideline recommends signposting of patients and families to charities and support groups. Documented examples include a local transplant teams support telephone line established during the pandemic by Anthony Nolan.[10]

NG164 recommends measures to mitigate risks of nosocomial transmission, including telephone or video consultations, avoiding non-essential clinic visits, coordinating blood tests and using alternative means of delivering medications. Many of these measures had been successfully implemented in centres across the UK.[11] Additionally, transplant centre healthcare workers are advised to follow UK guidance on infection prevention and control which includes the use of personal protective equipment (PPE) and recommendations on patient transfers, transport and options for outpatient settings.[12]

Patients with new symptoms of COVID-19

Patients undergoing HSCT are immunocompromised and may have atypical presentations of *SARS-CoV-2* infection.[13] They are also susceptible to other post-transplant complications which may have similar symptoms to COVID-19, including neutropenic sepsis or pneumonia caused by other pathogens. The expert panel was concerned that patients who feel unwell may be advised to isolate at home, which means that other types of infection or neutropenic sepsis—which is immediately life-threatening—could be missed. Consequently, the guideline recommends that patients with new symptoms suggestive of COVID-19 contact their transplant centre rather than the national NHS emergency telephone number, in order to receive specialist advice. The guidance also aligns with existing NICE guidance for people with cancer and suspected neutropenic sepsis, recommending assessment in secondary or tertiary care and offering immediate empirical antibiotic therapy (NICE CG151[14]).

Patients with symptoms suggestive of COVID-19 require testing for *SARS-CoV-2*. Isolation and the use of PPE are required until the test result is known.[15] If a patient tests positive for *SARS-CoV-2,* NG164 recommends following UK guidance on the management of exposed healthcare workers and patients in hospital settings, which includes information on testing and isolating patients.[15]

Transplant recipients pre-transplant

Transplant recipients are susceptible to viral infections, and evidence shows that respiratory viral infections can increase transplant-related mortality.[1] Recent evidence also suggests that this is true for HSCT patients who develop a *SARS-CoV-2* infection,[16-19] and advice includes social distancing, regular hand washing and self-isolation for the 14 days prior to admission. Patients should also be tested for *SARS-CoV-2* prior to admission regardless of whether they have symptoms, due to the high rate of asymptomatic carriers of the virus (reviewed in Ref. 20).

If patients have been in close contact with an individual infected with COVID-19 within the preceding week, deferral of transplant by three weeks was recommended. This recommendation was in line with EBMT guidance at that time, but since then the interval has been reduced to 'a minimum of 14 days' by the EBMT before the start of any transplant-related procedures and could be subject to further change.[3,5]

In patients with high-risk haematological disease progression, morbidity or mortality who test positive for *SARS-CoV-2*, it is recommended that transplant is deferred until they are asymptomatic and have three negative polymerase chain reaction (PCR) tests taken at least one week apart, similar to EBMT guidance which recommends two negative swabs, a deferral of 14 days from the first negative swab and a repeated swab prior to the start of conditioning.[3] In patients with lower risk disease it is suggested that their transplant is delayed by three months. A repeat assessment of organ function including a chest X-ray, echocardiogram and pulmonary function tests is recommended as organ function may have deteriorated due to the *SARS-CoV-2* infection.

Transplant donors

Following the initial rapid spread of *SARS-CoV-2*, the peak of infection in the general population occurred in mid-April 2020[21] with COVID-19 deaths peaking soon afterwards. Measures were required to reduce the risk and to mitigate the potential interruption to a planned transplant. For example, transplant centres and donor registries advised donors to follow government guidance on strict social distancing behaviour for at least four weeks before donating. Donors were advised to keep in contact with the harvest centre and to seek advice if they developed any symptoms suggestive of COVID-19. Due to the reported asymptomatic carriage of the virus by individuals, which ranges from 18%–88% depending upon the population studied,[22,23] screening by throat and nasal swabs for *SARS-CoV-2* PCR at least once prior to donation and ideally on the day of donation was recommended. Screening on the day of donation was

intended to provide an audit trail rather than inform the use of the harvested stem cells. In theory it was possible that a donor would be asymptomatic but positive for COVID-19 on the day of donation. There have been reports of *SARS-CoV-2* RNA being detected in several organs and in blood;[24] however, the presence of the potentially infectious virus in blood, and hence blood products, in an asymptomatic donor is remote.[25,26] The swab test on the day of donation would allow tracing in the event that a transplant recipient became unwell with COVID-19 post-transplant. Similarly, donors were asked to inform harvest teams if they developed any COVID-19 symptoms within two weeks of donation.[27]

A major change in the allogeneic transplant procedure was a recommendation by some donor registries to cryopreserve stem cells prior to the start of conditioning for the recipient, based on BSBMTCT recommendations and expert consensus.[3,4,27,28] The intention of this recommendation was to avoid the possibility that a donor was unable to donate due to developing COVID-19. Evidence from two retrospective studies indicated that the use of cryopreserved stem cells in allogeneic transplantation had no impact on transplant outcome.[29,30] If fresh cells were to be used, it was recommended that an alternative donor, including for haplo-identical or cord blood, was identified in case the selected donor was unable to donate.

Donors who had tested positive for COVID-19, even if asymptomatic, were required to be deferred for three months after the resolution of symptoms. This is longer than the period of 28 days recommended by the EBMT[3,5], but with evidence of long-term medical complications following COVID-19 the longer period of deferral seemed appropriate. However, it was recognised that in situations where the clinical urgency of the transplant was high then earlier donation would be possible with a risk assessment, an asymptomatic period and repeated negative swabs for *SARS-CoV-2* prior to donation.

Transplant recipients post-transplant

Based on the increased risk of mortality from other respiratory viruses[31], it was highly probable that transplant recipients would be at increased risk of mortality from *SARS-CoV-2*. Emerging evidence supports this assumption with data from the EBMT COVID-19 survey reporting the outcome of confirmed COVID-19 infection in 272 patients, 175 allogeneic SCT and 97 autologous SCT. The mortality rate was 30% in allogeneic recipients and 25·3% in autologous recipients.[17] A smaller report in 25 patients with haematological malignancies reported a mortality rate of 40% but only seven HSCT recipients were included in this study.[32] The CIBMTR registry has a cumulative reporting process and by the end of September 2020 a total of 554 cases of COVID-19 had been reported, with a mortality rate of 19·1%.[33] As with subgroups of patients with haematological malignancies, similar high mortality rates in HSCT recipients have been reported.[18,19] Strict social distancing behaviour was recommended in line with current guidelines.[3,4,12]

Supporting staff

Depletion of experienced transplant teams was acknowledged with staff remaining away from work, either due to symptomatic infection, contact with proven cases, or personal reasons.[12] The risk of nosocomial infection from staff was of great concern[34]; in the report by Malard, a large number of infections in patients with haematological malignancies were thought to have been acquired in hospital.[32] It was therefore important to ensure that transplant programmes could provide 'COVID-19 safe' environments with a key component being education of staff on the symptoms of COVID-19, regular symptom checks and routine screening of asymptomatic staff whenever possible. During the preparation of the guideline it was clear that there was uncertainty regarding the period that an individual may remain potentially infective, with reports of prolonged positivity by PCR despite resolution of symptoms.[24,35] Return to work recommendations from the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC) and EBMT indicated that staff should be asymptomatic, fever being the main symptom to have been resolved, have a minimum time-period since onset of symptoms and ideally two negative swabs for *SARS-CoV-2*.

The approach by the NICE guidelines group was pragmatic, acknowledging the rapidly changing evidence and limitations of testing.[36-40] Rivett *et al*. reported the results of a screening programme for asymptomatic staff in a large teaching hospital in the UK,[41] indicating that the presence or absence of symptoms alone would miss individuals still potentially shedding virus. Similar to the 'test-based strategy' of the CDC,[42] a recommendation was made for staff to be *asymptomatic* for at least seven days plus a negative *SARS-CoV-2* swab PCR test prior to returning to direct contact with transplant recipients.

The creation of 'COVID-19 safe' environments for transplant recipients was based on the provision of regular swab testing of staff. As of September 2020, PCR testing for *SARS-CoV-2* was limited and routine testing of asymptomatic staff was not achieved in all sites despite the NICE recommendation. A BSBMTCT survey of the 53 transplant units in the UK conducted in September 2020 received 42 responses; of these only 24 (57%) of centres were offering routine testing of asymptomatic staff with the majority (83%) using nose and throat swab tests for *SARS-CoV-2* (Bloor *et al*., BJH 2020 accepted).

Prioritising treatment

Given the uncertainties during the early phase of the COVID pandemic, there was a need to prioritise HSCT procedures

depending on risk of disease indication if untreated by HSCT, and potential risk of severe COVID-19 infection during and after HSCT. To inform shared decision-making with patients, NICE recommended that multidisciplinary teams (MDTs) consider using transplant outcome predictive tools such as the haematopoietic cell transplantation-specific comorbidity index (HCT-CI)[43,44] or the refined disease risk index (DRI),[45] but also to be aware of the limitations of these tools. Prioritising treatment for people with high risk of haematological disease progression, morbidity or mortality enabled units to focus on critically urgent, curative HSCT procedures concentrated in larger units where COVID-19-minimised pathways could be provided. Close liaison within local MDTs was recommended to consider suitable alternative treatments if the risks associated with COVID-19 were felt to be higher than the risk of continuing with the transplant.

Modifications to usual care

NICE recommended different ways of working within HSCT programmes, as well as regional (adults) and national (paediatrics) via 'clusters' of HSCT centres within operational delivery networks (ODNs) to provide a 'safety net' should any programmes fail to maintain quality standards and/or meet demands in activity. ODNs were extended to support devolved nations. Modifications to haematopoietic stem cell collection (apheresis and bone marrow harvest) practice and facilities were also recommended. Engagement between stakeholders was critical,[3,5,27,46,47] along with reporting into the EBMT registry experience.[17]

Impact of COVID-19 on HSCT activity in the UK

Table I and Fig 1A,B summarise the autologous and allogeneic HSCT activity (adult and paediatric combined) as reported to the BSBMTCT registry during the period 1 Jan–31 July in 2019 and 2020. Both autologous and allogeneic HSCT activity fell in March 2020, reaching a nadir in April 2020, which corresponded with the peak of the COVID-19 crisis in the UK. Autologous HSCT was reduced to a greater extent than allogeneic HSCT, reaching 16·4% of the 2019 activity, while allogeneic HSCT fell to 65%.

Table I. Day 0 transplant registrations received by the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) Registry for the period 1 January–31 July in 2019 compared with 2020. The numbers include adult and paediatric transplant activity.

	January	February	March	April	May	June	July
AutoSCT							
2019	227	216	234	220	265	216	248
2020	221	197	146	36	80	82	143
%	97·4	91·2	62·4	16·4	30·2	38·0	57·7
AlloSCT							
2019	144	129	135	147	138	123	151
2020	132	120	103	65	89	87	72
%	91·7	93	76·3	44·2	64·5	70·7	47·7

These data show the total transplant activity in the UK but there was considerable heterogeneity of the impact around the country; some small autologous HSCT units ceased all activity, and some large programmes reduced autologous HSCT activity but maintained allogeneic activity close to 2019 levels, while some large programmes reduced both (BSBMTCT registry data). The impact of the COVID-19 crisis on individual centres was influenced by several factors, including local infection rates, staffing levels and risk assessments. The reduction of transplant activity, particularly for autologous HSCT, created a large 'backlog' of patients awaiting transplantation, and, by the time of the second wave of the pandemic, HSCT in the UK was still in recovery phase as activity had still not reached that of 2019.

Conclusion

The COVID-19 pandemic has posed an exceptional challenge for the stem cell transplant community which responded quickly by publishing relevant guidance for the management of transplant recipients, advice on safe service delivery and donor issues[4], and was updated in response to new evidence and government advice. The advice and experience from experts within EBMT was invaluable in formulating these guidelines.[3] The NHS also responded quickly to the complex issues posed by the pandemic to support patients, NHS trusts, clinicians and commissioners. The guidelines will require ongoing review as more clinical evidence emerges and government advice changes to address further 'waves' of the pandemic, and, ultimately, the challenge of 'endemic' COVID-19.

Acknowledgements

All the authors actively contributed as per ICMJE authorship requirements. NICE NG164 was developed, published (1 April 2020) and updated (29 July 2020) by EM, MD, AP and PS, with clinical input led by JAS, KO and FLD on behalf of NHSE&I Clinical Reference Group (CRG) for Blood and Marrow Transplantation and BSBMTCT. The BSBMTCT Head of Registry and Statistician (JL & RP) provided data, statistical analysis and interpretation of the registry data, with clinical input from KO, JAS and FD. All authors wrote, reviewed and approved the manuscript.

NICE NG164 was produced by NICE as part of the response of NHSE&I to the COVID-19 pandemic. JAS and FLD receive remuneration from NHSE&I for chairing the CRG. BSBMTCT maintains the national registry with data management and statistical support (JL and RP). All patients have consented for data entry into the registry in accordance with data protection regulations.

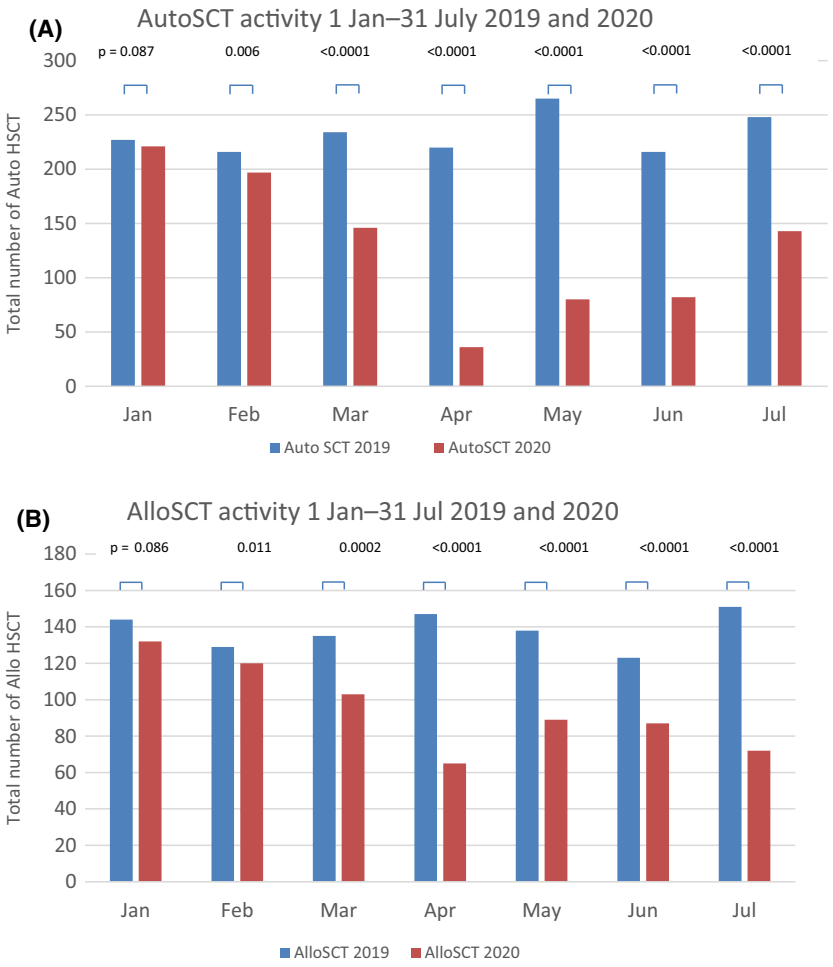

Fig 1. (A) Day 0 reported autologous HSCT activity in the period 1 January–31 July, comparing monthly totals for 2019 and 2020. *P*-values were determined from a linear regression model using monthly data for 2007–2019, assuming normally distributed variation. (B) Day 0 reported allogeneic HSCT activity in the period 1 January–31 July, comparing monthly totals for 2019 and 2020. *P*-values were determined from a linear regression model using monthly data for 2007–2019, assuming normally distributed variation. [Colour figure can be viewed at wileyonlinelibrary.com]

The authors wish to thank the executive committee of the BSBMTCT for their contribution to these guidelines: Deborah Richardson, Dominic Culligan, Kavita Raj, Maria Gilleece, Eduardo Olavarria, Marie Waller, Bim Laguda, Rachael Hough, Ram Malladi, Jennifer Byrne, Matthew Collin, Stephen Robinson. The authors would also like to thank the UK and Ireland Paediatric BMT Group (chair, Persis Amrolia), UK Myeloma Forum (John Ashcroft and Gordon Cook) and other stakeholder groups who contributed to development and updating of NG164.

The authors also wish to thank Janette Harper and Rob Coster from NHSE&I for their contribution to these guidelines and all members of the NHSE&I Clinical Reference Group for Blood and Marrow Transplantation, and Henny Braund, Amelia Chong, Rob Danby and members of the Anthony Nolan team, who have supported regular video-conferenced discussions throughout the pandemic.

Conflicts of interest

JAS was chair of BMT-CRG from June 2016–June 2020, and FLD is chair from April 2020. They co-chaired the BMT-CRG from April–June 2020. KO was President of BSBMTCT from January 2018 to December 2020, and JS is President from January 2021–December 2022. No other conflicts of interest were declared.

References

1. Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*. 2014;**59**(Suppl 5):S344–S351.
2. NICE. COVID-19 rapid guideline: haematopoietic stem cell transplantation [updated 29/07/2020]. Available from: https://www.nice.org.uk/guidance/ng164
3. Ljungman P, Mikulska M, de la Camara R, Basak GW, Chabannon C, Corbacioglu S, et al. The challenge of COVID-19 and hematopoietic cell

transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. *Bone Marrow Transplant*. 2020;**55**:2071–6.
4. BSBMTCT. BSBMT&CT recommendations for the management of adult patients and allogeneic donors during the COVID-19 (causative agent the SARS-CoV-2 virus) outbreak. 2020 [16.05.2020]. Available from: http://www.BSBMTCT.org/wp-content/uploads/2020/05/BSBMTCT-recommendations-for-COVID_May2020_ver3.0-FINAL.pdf
5. Ljungman P, Styczynski J, Mikulska M, de la Camara R. CORONAVIRUS DISEASE COVID-19: EBMT RECOMMENDATIONS [website]. ebmt; 2020 [updated 23 Dec 2020; cited 2020 Dec 27]. Available from: https://www.ebmt.org/covid-19-and-bmt
6. NICE. Developing NICE guidelines: the manual 2014 [updated 17/07/2020; cited 2020]. Available from: https://www.nice.org.uk/process/pmg20/resources/appendix-l-interim-process-and-methods-for-guidelines-developed-in-response-to-health-and-social-care-emergencies-8779776589/chapter/introduction-and-overview
7. NICE. Research to access pathway for investigational drugs for COVID-19 (RAPID-C19). 2020. Available from: https://www.nice.org.uk/covid-19/rapid-c19
8. Lee SJ, Loberiza FR, Antin JH, Kirkpatrick T, Prokop L, Alyea EP, et al. Routine screening for psychosocial distress following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;**35**(1):77–83.
9. ONS. Office for National Statistics: Impact of the coronavirus pandemic on the mental health of clinically extremely vulnerable people [Web page]. [updated 29/06/2020]. Available from: https://www.ONS.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/coronavirusandshieldingofclinicallyextremelyvulnerablepeopleinengland/9juneto18june2020#impact-of-the-coronavirus-pandemic-on-the-mental-health-of-clinically-extremely-vulnerable-people
10. Nolan A. Telephone Emotional Support [cited 2020 Dec 27]. Available from: https://www.anthonynolan.org/patients-and-families/get-support-us/telephone-emotional-support
11. Willan J, King AJ, Hayes S, Collins GP, Peniket A. Care of haematology patients in a COVID-19 epidemic. *Br J Haematol*. 2020;**189**(2):241–3.
12. PHE. Protect yourself and others from coronavirus 2020. Available from: https://www.gov.uk/coronavirus
13. Zhou X, Wang G, Chen L, Meng F, Huang L, Huang L, et al. Clinical characteristics of hematological patients concomitant with COVID-19. *Cancer Sci*. 2020;**111**(9):3379–85.
14. NICE. NICE guideline on neutropenic sepsis: CG151 2012. Available from: https://www.nice.org.uk/guidance/cg151
15. PHE. COVID-19: infection prevention and control (IPC) gov.uk: HM Government UK; 2020 [updated 16/09/2020]. Available from: https://www.gov.uk/government/publications/wuhan-novel-coronavirus-infection-prevention-and-control
16. Passamonti F, Cattaneo C, Arcaini L, Bruna R, Cavo M, Merli F, et al. Clinical characteristics and risk factors associated with COVID-19 severity in patients with haematological malignancies in Italy: a retrospective, multicentre, cohort study. *Lancet Haematol*. 2020;**7**(10):e737–e745.
17. Ljungman P, de la Camara R, Mikulska M, Tridello G, Aguado B, Beguin Y, et al. COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. EBMT Annual Meeting; 29.08.2020; Madrid.
18. Shah V, Ko Ko T, Zuckerman M, Vidler J, Sharif S, Mehra V, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. *Br J Haematol*. 2020;**190**(5):e279–e282.
19. Piñana JL, Martino R, García-García I, Parody R, Morales MD, Benzo G, et al. Risk factors and outcome of COVID-19 in patients with hematological malignancies. *Exp Hematol Oncol*. 2020;**9**:21.
20. Huff HV, Singh A. Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies. *Clin Infect Dis*. 2020:ciaa654.
21. PHE. Coronavirus (COVID-19) in the UK 2020 [updated 03/10/2020]. Available from: https://coronavirus.data.gov.uk
22. Nikolai LA, Meyer CG, Kremsner PG, Velavan TP. Asymptomatic SARS Coronavirus 2 infection: invisible yet invincible. *Int J Infect Dis*. 2020;**100**:112–6.
23. Aguilar JB, Faust JS, Westafer LM, Gutierrez JB. A Model Describing COVID-19 Community Transmission Taking into Account Asymptomatic Carriers and Risk Mitigation. *medRxiv*. 2020; 2020.03.18.20037994.
24. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ (Clinical research ed)*. 2020;**369**:m1443.
25. Corman VM, Rabenau HF, Adams O, Oberle D, Funk MB, Keller-Stanislawski B, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. *Transfusion*. 2020;**60**(6):1119–22.
26. Katz LM. Is SARS-CoV-2 transfusion transmitted? *Transfusion*. 2020;**60**(6):1111–4.
27. JPAC. Joint UKBTS Professional Advisory Committee: Position statement: SARS-CoV-2/COVID-19 and the safety of Blood, Tissues and Stem Cells. 2020. Available from: https://www.transfusionguidelines.org/document-library/documents/jpac-position-statement-sars-cov-2-covid-19-june-2020-pdf
28. WMDA. Coronavirus - SARS-CoV-2 & COVID-19 2020 [updated 14/08/2020]. Available from: https://share.wmda.info/pages/viewpage.action?pageId=344866320#/
29. Medd P, Nagra S, Hollyman D, Craddock C, Malladi R. Cryopreservation of allogeneic PBSC from related and unrelated donors is associated with delayed platelet engraftment but has no impact on survival. *Bone Marrow Transplant*. 2013;**48**(2):243–8.
30. Hamadani M, Zhang MJ, Tang XY, Fei M, Brunstein C, Chhabra S, et al. Graft cryopreservation does not impact overall survival after allogeneic hematopoietic cell transplantation using post-transplantation cyclophosphamide for graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant*. 2020;**26**(7):1312–7.
31. Ljungman P, Ward KN, Crooks BN, Parker A, Martino R, Shaw PJ, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2001;**28**(5):479–84.
32. Malard F, Genthon A, Brissot E, van de Wyngaert Z, Marjanovic Z, Ikhlef S, et al. COVID-19 outcomes in patients with hematologic disease. *Bone Marrow Transplant*. 2020;**55**:2180–4.
33. CIBMTR. COVID-19 Reported Data 2020. Available from: https://www.CIBMTR.org/Covid19/Pages/default.aspx
34. Rickman HM, Rampling T, Shaw K, Martinez-Garcia G, Hail L, Coen P, et al. Nosocomial transmission of COVID-19: a retrospective study of 66 hospital-acquired cases in a London teaching hospital. *Clin Infect Dis*. 2020;**20**:ciaa816.
35. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;**382**(10):970–1.
36. Afzal A. Molecular diagnostic technologies for COVID-19: limitations and challenges. *J Adv Res*. 2020;**26**:149–59.
37. Xiao AT, Tong YX, Zhang S. False negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence. *J Med Virol*. 2020;**92**:1755–6.
38. Cárdenas-Camarena L, Bayter-Marin JE, Durán H, Hoyos A, López-Romero CO, Robles-Cervantes JA, et al. Elective surgery during SARS-Cov-2/COVID-19 pandemic: safety protocols with literature review. *Plast Reconstr Surg*. 2020;**8**(6):e2973.
39. Gruskay JA, Dvorzhinskiy A, Konnaris MA, LeBrun DG, Ghahramani GC, Premkumar A, et al. Universal testing for COVID-19 in essential orthopaedic surgery reveals a high percentage of asymptomatic infections. *J Bone Joint Surg Am*. 2020;**102**(16):1379–88.
40. Kader N, Clement ND, Patel VR, Caplan N, Banaszkiewicz P, Kader D. The theoretical mortality risk of an asymptomatic patient with a negative

SARS-CoV-2 test developing COVID-19 following elective orthopaedic surgery. *Bone Joint J*. 2020;**102-b**(9):1256–60.
41. Rivett L, Sridhar S, Sparkes D, Routledge M, Jones NK, Forrest S, et al. Screening of healthcare workers for SARS-CoV-2 s the role of asymptomatic carriage in COVID-19 transmission. *eLife*. 2020;**9**:e58728.
42. CDC. Centre for Disease Control: Interim Guidance on Testing Healthcare Personnel for SARS-CoV-2 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-healthcare-personnel.html
43. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;**106**(8):2912–9.
44. Sorror ML, Storb RF, Sandmaier BM, Maziarz RT, Pulsipher MA, Maris MB, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2014;**32**(29):3249–56.
45. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;**123**(23):3664–71.
46. JACIE. FACT-JACIE International Standards for Hematopoietic Cellular Therapy. 2018 [updated 01/06/2018]. 7.0. Available from: https://www.ebmt.org/accreditation/jacie-standards
47. Anthony Nolan response to COVID-19 2020. Available from: https://www.anthonynolan.org/anthony-nolan-response-covid-19

